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Overlap syndrome: Additive effects of COPD on the cardiovascular damages in patients with OSA

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Hypoxia;
Inflammation

Summary
The chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) have been recently much focused as independent risks for cardiovascular disease. Furthermore, the complication of both has a worse prognosis compared with patients with only one of these diseases. However, the details of the underlying mechanisms of this worsened prognosis have not been clear. The cross-sectional study was conducted to examine whether the overlap of COPD augment the increase in arterial stiffness in subjects with OSA. If so, we examined the exaggeration of nocturnal hypoxemia and its related inflammation are related to this augmentation of increased arterial stiffness. In 524 male subjects with OSA diagnosed by polysomnography (apnea–hypopnea index >5/h) (52 ± 14 years old), the forced expiratory volume at 1 s/the forced vital capacity (FEV_1/FVC) ratio, brachial-ankle pulse wave velocity (baPWV), blood C-reactive protein (CRP) and B-natriuretic peptide (BNP) levels were measured. The prevalence rate of COPD was 12% in this study subjects. Plasma BNP levels and the crude (median value, 17.2 vs. 14.1 m/s, $p < 0.01$) and adjusted value of baPWV were significantly higher in subjects with overlap syndrome than in those with OSA alone. However, parameters of nocturnal hypoxemia and serum CRP levels were similar between both groups. Thus, the overlap of COPD in patients with OSA augments increase in arterial stiffness without the exaggeration of nocturnal hypoxemia and inflammation. Even so, this augmentation may partially contribute to the increased cardiovascular risk in the overlap syndrome.

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Introduction

Several studies have demonstrated that increased arterial stiffness acts as an independent risk factor for cardiovascular disease via several mechanisms.[1–3] Obstructive sleep apnea (OSA) has also drawn much attention as an independent risk factor for cardiovascular disease.[4,5] In patients with OSA, arterial stiffness is increased[6–8] and therefore, this increase is thought to have some contribution to the increased cardiovascular risk in these patients. On the other hand, arterial stiffness is also increased in patients with chronic obstructive pulmonary disease (COPD), an independent risk factor for cardiovascular disease.[9] Previous studies have suggested that the prevalence of COPD in patients with OSA was, respectively, of 11%[10] and 14%,[11] therefore, overlap coexistence of the two conditions is not rare in clinical settings. Patients with the overlap syndrome have a worse prognosis as compared with patients with only one of these diseases.[12,13] While the underlying mechanisms of this worsened prognosis have not yet been fully clarified, it is possible that accelerated arterial stiffening contributes to the overlap-related worsening of the prognosis in the overlap syndrome.

The present cross-sectional study was conducted to examine whether the overlap of COPD might augment the increased arterial stiffness in subjects with OSA. If so, we examined the exaggeration of nocturnal hypoxemia and its related inflammation are related to this augmentation of increased arterial stiffness.

Methods

Study patients

We evaluated all eligible patients from 756 consecutive patients who underwent overnight polysomnography (PSG) at Tokyo Medical University Hospital from November 2004 to April 2009. The exclusion criteria were: women (because of the small number of study subjects) ($n = 121$), AHI <5.0 ($n = 11$), presence of cardiovascular disease {ischemic heart disease, valvular heart disease, cardiomyopathy, atrial fibrillation, stroke, arteriosclerosis obliterans, aortic aneurysm, pulmonary embolism, and a left ventricular ejection fraction (LVEF) of less than 40%} ($n = 72$), renal insufficiency (serum creatinine level >176.8 μmol/L) ($n = 8$), serum C-reactive protein level >1.0 mg/L ($n = 8$), and subjects with restrictive pulmonary disease {percent predicted forced vital capacity (FVC) $<80\%$} ($n = 12$). Finally, 524 patients were successfully entered in the final analysis (Fig. 1). The study was conducted with the approval of the Ethics Committee of Tokyo Medical University, and written informed consent was obtained from each of the subjects prior to their participation in the study.

Sleep study

Overnight, fully-attended PSG monitoring was performed with the Alice 4 Sleep System™ (Respironics, Inc., Murrysville, PA) in the sleep laboratory. The sleep stages were monitored by electroencephalography, electrooculography and electromyography, according to standard criteria,[14–16] and arousals were defined according to the standard criteria of the American Academy of Sleep Medicine.[14–16] Oronasal airflow was measured with a thermistor, thoracoabdominal movements were monitored with a strain gauge, and the oxyhemoglobin saturation (SpO2) in the blood was monitored by pulse oximetry. Then, the mean nocturnal oxygen transcutaneous saturation (meanSpO2), minimal nocturnal oxygen transcutaneous saturation (minSpO2), and recording time spent at nocturnal oxygen transcutaneous saturation $<90\%$ (timeSpO2 $<90\%$) were obtained as markers of nocturnal hypoxemia. The respiratory events and sleep stage were scored manually.[14–16] Apnea was defined as cessation of oronasal airflow for 10 s or more, and hypopnea was defined as a 50% or greater decrease in oronasal airflow lasting for more than 10 s associated with a 3% or greater decrease in arterial oxygen saturation relative to the baseline level. Obstructive apnea/hypopnea was defined as the significant apnea/hypopnea in the presence of thoraco-abdominal effort, and central apnea/hypopnea was defined as significant apnea/hypopnea in the absence of oronasal air flow or thoracoabdominal effort.[14–16] The apnea–hypopnea index (AHI) was calculated as the total number of apnea and hypopnea episodes per hour of sleep. Patients were defined as having OSA when the obstructive component was dominant and the AHI was ≥ 5 per hour. The severity of OSA was classified according the criteria of the American Academy of Sleep Medicine (i.e., AHI 5–14 per hour = mild; 15–30 per hour = moderate; ≥ 30 per hour = severe).[14–16]

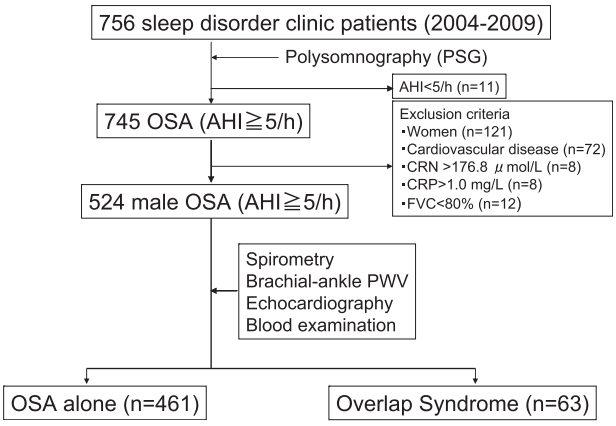

Figure 1 Study protocol. OSA = obstructive sleep apnea; AHI = apnea–hypopnea index; CRN = serum creatinine level; CRP = serum C-reactive protein level; FVC = forced vital capacity; PWV = pulse wave velocity.

Pulmonary function

Pulmonary function was measured with a volume-displacement, water-sealed spirometer (SP-750, Fukuda Co. Ltd, Tokyo, Japan), based on a forced vital capacity maneuver, in which the subject was requested to exhale the maximal volume of air during a forced expiratory maneuver starting from a position of full inspiration and ending at complete expiration. The forced expiratory

volume at 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were examined. The coefficient of variation of the FEV_1/FVC ratio was 2.9% at our institute. The measurements were conducted by trained technicians.

Overlap syndrome was defined according to McNicholas's report.[17] An FEV_1/FVC ratio of >70% plus FVC >80% was defined as pulmonary function within the normal range. Overlap syndrome was defined as AHI ≥5 per hour with an FEV_1/FVC ratio of ≤70% plus FVC >80%. On the other hand, the severity of COPD was graded as follows: mild = FEV_1 >80% predicted; moderate = FEV_1 50–79% predicted; severe = FEV_1 <50% predicted.[18]

Echocardiogram

M-mode echocardiograms were obtained by two-dimensional echocardiography using an echocardiography instrument equipped with a 3.0-MHz to 5.0-MHz transducer. The mean of two M-mode measurements obtained by two investigators was used. The left ventricular mass was calculated by Deveroux's method.[19] The left ventricular mass index (LVMI) was estimated as the left ventricular mass divided by the body surface area. Left ventricular systolic and diastolic volumes and LVEF were derived from the M-mode images, according to standard criteria.[20] Pulsed Doppler measurements of the left ventricular diastolic inflow were obtained by two-dimensional echo-guidance. Briefly, the left ventricular diastolic filling pattern was recorded from the apical transducer position in patients in the partial left lateral decubitus position during expiratory apnea, the sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity) were recorded, and the E/A ratio and deceleration time (DCT) were calculated as the interval from the E-wave peak to the decline of the velocity to the baseline values obtained from 3 consecutive cardiac cycles.

Brachial-ankle pulse wave velocity

The brachial-ankle PWV (baPWV) was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan), in accordance with a previously described methodology.[21,22] Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached to the left chest. Electrocardiograms and phonocardiograms were used to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles while the subjects lay in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms determined by the plethysmographic sensor and recorded for 10 s were stored. The measurements were conducted after the subjects had rested for at least 5 min in the supine position, in an air-conditioned room[24–26] earmarked exclusively for this purpose. The blood pressure determined by the oscillometric sensor and the heart rate was simultaneously obtained during measurement of the baPWV.

Laboratory measurements

The serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG), creatinine (CRN), and the fasting plasma glucose (FPG) were measured enzymatically in blood samples obtained from the subjects after they had fasted overnight.

Statistical analysis

Since the deviation of AHI and FEV_1/FVC ratio were skewed, the values of these variables were log-transformed for the analysis in this study. The normality of the distribution of the variables was assessed by the Kolmogorov–Smirnov test. Then, the variables that showed normal distribution were represented as mean ± SD, and those that did not show normal distribution were represented as the median (25th–75th percentile) values, as shown in Table 1.

The relationships of the baPWV with other variables were assessed by univariate linear regression analysis and multivariate linear regression analysis. In these analyses, the variables not showing normal distribution were log-transformed. For the adjustments, a Basic Adjustment Model was used, with the smoking status (non- or past smoker = 0, current smoker = 1), age, TC, log-transformed variables (body mass index, mean blood pressure, heart rate, HDL, TG, CRN, FPG and AHI) and history/no history of medication for hypertension, diabetes mellitus and/or dyslipidemia (this factor was assigned a score of 1 for the presence of a history of medication and 0 for the absence of a history of medication) as the covariates. Thus, the details of the drug types prescribed were not considered and the adjustment was applied for the drug classes as a composite.

For assessment of the differences in the status of each variable among the groups, Kruskal–Wallis test for continuous variables and Pearson's chi-squared test for categorical variables were applied. Furthermore, for assessment of the differences in the status of the baPWV among the groups, a general linear model (GLM) analysis with adjustments was applied. Covariates that were adjusted for were similar to those mentioned for the multivariate linear regression analyses. All the analyses were conducted using the SPSS software for Windows, version 11.0J (SPSS, Chicago, IL); P values <0.05 were considered to denote statistical significance.

Results

The Kolmogorov–Smirnov test demonstrated that only age and TC were normally distributed, while other variables such as the baPWV, AHI, FEV_1/FVC ratio, and FEV_1 were not normally distributed showed skewed distribution. The prevalence rate of COPD was 12% in this study subjects. The clinical characteristics of the study subjects with OSA alone and those with overlap syndrome are described in Table 1. The age and serum BNP levels were higher and the BMI and ESS were lower in subjects with overlap syndrome than in those with OSA alone, however, the serum CRP levels was similar between the two groups (Table 1). In the entire study population, 57% (296/524 men) were categorized as

Table 1 Clinical characteristics of the patients with OSA alone and overlap syndrome.

	OSA alone $n = 461(88\%)$	Overlap $n = 63$ (12%)	P value
Age (yr)	48.6 ± 12.8	63.9 ± 11.7	<0.01
BMI (kg/m^2)	26.0 (23.7–28.5)	24.8 (23.4–26.1)	0.04
Current Smoker, *n* (%)	201 (44)	29 (46)	0.40
SBP (mmHg)	126 (117–134)	127 (119–137)	0.46
DBP (mmHg)	76 (69–82)	76 (70–84)	0.97
TC (mmol/L)	5.3 ± 0.9	5.1 ± 0.8	0.13
HDL (mmol/L)	1.2 (1.1–1.5)	1.2 (1.1–1.6)	0.91
TG (mmol/L)	1.8 (1.3–2.5)	1.5 (1.1–2.2)	0.10
FPG (mmol/L)	4.9 (4.5–5.5)	5.1 (4.7–5.6)	0.25
CRN (μmol/L)	72.3 (64.2–80.3)	74.0 (67.8–83.8)	0.16
BNP (pg/dl)	10.9 (5.3–20.8)	20.8 (9.7–57.0)	<0.01
CRP (mg/dl)	0.06 (0.03–0.14)	0.07 (0.03–0.19)	0.32
ESS	9.0 (6.0–13.0)	7.0 (4.5–11.0)	<0.01
Medication, *n* (%)			
Hypertension	37 (8)	6 (10)	0.63
Diabetes mellitus	32 (7)	3 (5)	0.79
Dyslipidemia	73 (16)	16 (25)	0.07
FEV_1/FVC ratio (%)	80.1 (76.7–84.0)	66.5 (63.1–68.7)	<0.01
FEV_1 (% predicted)	90.7 (84.8–98.6)	79.9 (68.4–90.4)	<0.01
Severity of COPD, *n* (%)			
Mild		34 (54)	
Moderate		27 (43)	
Severe		2 (3)	
LVEF (%)	67.0 (64.0–70.0)	67.0 (63.0–71.0)	0.12
FS (%)	37.0 (35.0–40.0)	37.0 (34.0–40.0)	0.25
LVMI (g/m^2)	120.4 (108.1–139.2)	129.4 (111.9–141.5)	0.11
DCT (s)	195.0 (171.0–221.0)	220.0 (190.0–254.0)	<0.01
E/A ratio	1.29 (1.07–1.50)	0.84 (0.65–1.01)	<0.05
baPWV (m/s)	14.1 (12.8–15.8)	17.2 (14.1–19.5)	<0.01

Abbreviations: OSA = obstructive sleep apnea; Overlap = patients with OSA and chronic obstructive pulmonary disease; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; HDL = serum high density lipoprotein cholesterol; TG = serum triglycerides; FPG = fasting plasma glucose; CRN = serum creatinine concentration; BNP = B-type natriuretic peptide; CRP = serum C-reactive protein levels; ESS = Epworth sleepiness scale; FEV_1/FVC ratio, the forced expiratory volume at 1 s (FEV_1) and the forced vital capacity (FVC) ratio; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; FS = fractional shortening; LVMI = left ventricular mass index; DCT = deceleration time; E/A = the peak velocity of early rapid filling (E velocity)/the peak velocity of atrial filling (A velocity); baPWV = brachial-ankle pulse wave velocity.

having severe OSA, whereas in the subjects with the overlap syndrome, most were categorized as having mild/moderate COPD (Table 1). In sleep study, total sleep time, sleep efficiency and stage 3/4 sleep% were lower in subjects with overlap syndrome than in those with OSA alone, but parameters of nocturnal hypoxemia were similar between the two groups (Table 2).

In the present study, most of the subjects with overlap syndrome had mild to moderate COPD, and only two subjects had severe COPD.

In vascular function test, baPWV and DCT were significantly higher and E/A ratio was significantly lower in subjects with overlap syndrome than in those with OSA alone. However, the LVEF, FS and LVMI were similar between the two groups (Table 1). The difference in the baPWV was significant even after the adjustments for the covariates and AHI (the covariates are described in detail in the statistics section) (Fig. 2).

The log-transformed baPWV had a significant correlation with log-transformed AHI (correlation co-efficient = 0.21, $P < 0.01$), log-transformed FEV_1/FVC ratio (correlation co-efficient = −0.35, $P < 0.01$) and log-transformed FEV_1 (correlation co-efficient = −0.12, $P < 0.01$). The log-transformed AHI and log-transformed FEV_1/FVC ratio were entered simultaneously into the multivariate linear regression analysis. Then, multivariate linear regression analysis demonstrated a significant relation between the log-transformed FEV_1/FVC ratio and the log-transformed baPWV, independent of the covariates and log-transformed AHI (Table 3). When the log-transformed FEV_1 (rather than the log-transformed FEV_1/FVC ratio) was entered in this multivariate model, it was identified as a significant factor influencing the baPWV (R-square = 0.55; standardized coefficient = −0.094, $P < 0.05$). The log-transformed FEV_1/FVC ratio showed no significant correlation with log-transformed AHI (correlation co-efficient = −0.006,

Table 2 Sleep study.

	OSA alone $n = 461$	Overlap $n = 63$	P value
AHI	33.7 (20.3—53.9)	30.9 (20.2—51.3)	0.18
meanSpO2, %	95.0 (94.0—96.0)	95.0 (93.0—96.0)	0.63
minSpO2, %	81.0 (74.0—86.0)	81.0 (77.0—86.0)	0.18
timeSpO2 <90%, %	1.7 (0.3—7.7)	2.1 (0.2—5.6)	0.13
Desaturation index	27.3 (13.1—47.7)	23.2 (11.3—43.5)	0.09
Total sleep time, min	451 (405—489)	428 (400—465)	<0.01
Sleep efficiency, %	83.9 (76.1—88.9)	78.5 (70.8—86.2)	<0.01
Stage 1 sleep, %	26.3 (17.5—38.2)	29.7 (22.2—36.8)	0.66
Stage 2 sleep, %	50.5 (42.0—57.7)	50.8 (43.1—55.5)	0.76
Stage 3/4 sleep, %	1.7 (0.1—5.5)	0.6 (0.0—3.4)	<0.01
Stage REM sleep, %	18.2 (14.1—21.8)	17.4 (13.3—21.1)	0.38
Arousal index	36.8 (26.1—54.6)	38.2 (27.4—48.2)	0.09

Abbreviations: AHI = apnea—hypopnea index; meanSpO2 = mean nocturnal oxyhemoglobin saturation; minSpO2 = the minimal nocturnal oxyhemoglobin saturation; timeSpO2 <90% = recording time spent at nocturnal oxyhemoglobin saturation <90%; REM = rapid eye movement.

$P = 0.89$), the log-transformed minSpO2 (correlation co-efficient = 0.02, $P = 0.66$), the log-transformed meanSpO2 (correlation co-efficient = −0.06, $P = 0.20$), the log-transformed timeSpO2 <90% (correlation co-efficient = 0.07, $P = 0.10$), or log-transformed serum CRP levels (correlation co-efficient = 0.01, $P = 0.75$). Furthermore, these parameters of nocturnal hypoxemia were similar between the two groups (Table 1).

Discussion

The present study was conducted to evaluate the effect of overlap by COPD on the rate of arterial stiffness in subjects with OSA. OSA and COPD represent two of the most prevalent chronic respiratory disorders.[10,12,13] Both disorders are associated with increased arterial stiffness,[6–9] but the their interaction has not yet been clarified. In the present study, a significant correlation was observed between the FEV_1/FVC ratio, a marker of pulmonary dysfunction,[17] and the baPWV, independent of the AHI, a marker of the severity of OSA[14–16]; the baPWV was significantly higher in subjects with overlap syndrome than in those with OSA alone. Thus, while several studies have reported that OSA itself increases arterial stiffness,[6,7] the present study is the first to suggest that overlap by COPD is one of the key elements underlying the increase in arterial stiffness in subjects with OSA.

In the present study, 12% of the study subjects with OSA had COPD, and the prevalence rate was consistent with previous reports.[10,11] Overlap by COPD is not rare in patients with OSA, and patients with the overlap syndrome have a lower 5-year survival than patients with OSA alone.[10,12,13] Arterial stiffness is thought to act as a cardiovascular risk factor via causing increased cardiac afterload, impaired coronary blood supply, increase in shear stress on the vascular endothelium (i.e., direct atherogenic action), microvascular damage, and so on.[1–3] Increased cardiac afterload elevates the serum levels of BNP and causes left ventricular hypertrophy.[23] We previously reported that increase of arterial stiffness is associated with elevation of the serum BNP levels in the general population.[24] In the present study, the serum levels of BNP were higher in subjects with overlap syndrome than in those with OSA alone,

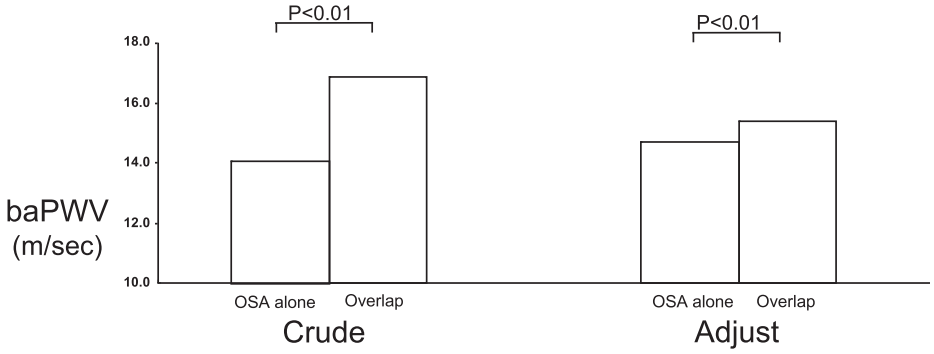

Figure 2 Crude and adjusted values of the baPWV in subjects with OSA alone and those with the overlap syndrome. baPWV = brachial-ankle pulse wave velocity; values are presented as the median (25th—75th percentile) values. The smoking status, age, TC, log-transformed variables (body mass index, mean blood pressure, heart rate, HDL, TG, CRN, FPG and AHI) and history of medication (hypertension, diabetes mellitus and dyslipidemia) were included in the model as the covariates.

Table 3 Univariate and multivariate linear regression analysis to access relationship with log-transformed baPWV.

	Univariate		Multivariate (R-square = 0.57)		
	r	P value	Non-standardized co-efficient (95% CI)	Standardized co-efficient	P value
log FEV_1/FVC ratio	−0.35	<0.01	−0.109 (−0.193 to −0.025)	−0.091	<0.05
log AHI	0.21	<0.01	0.007 (−0.01−0.024)	0.029	0.40

Abbreviations: CI = confidence interval.
As described in the footnote for Table 1; the smoking status, age, TC, log-transformed variables (body mass index, mean blood pressure, heart rate, HDL, TG, CRN, FPG and AHI) and history/no history of medication for hypertension, diabetes mellitus and/or dyslipidemia as the covariates.

although the LVMI was similar between the two groups. Thus, the results of the present study suggest that augmented increase in arterial stiffness in the overlap syndrome may contribute, at least in part, to the overlap-related increase in cardiovascular risk. Hypoxemia and inflammation can increase arterial stiffness.[9,17,25,26]

Lacedonia et al.[27] reported that patients with overlap syndrome present a high percentage of neutrophils in induced sputum like patients affected by COPD or OSA alone, however, the serum CRP, a marker of inflammation, was similar between the two groups. While it is known that overlap by COPD produces greater sleep disturbance and oxygen desaturation than OSA alone,[28] nocturnal hypoxemia was not exaggerated in the subjects with overlap syndrome in the present study. One of the plausible reason for this discrepancy might be that most of the present study subjects with the overlap syndrome had only mild to moderate COPD, and COPD of milder severity may not be associated with worsened nocturnal hypoxemia. The present study demonstrated that the overlap of OSA by such mild/moderate COPD may be associated with accelerated arterial stiffening without worsening of the nocturnal hypoxemia and inflammation.

The present study had some limitations, as follows: 1. Age and obesity are major determinants of increase in the arterial stiffness.[29,30] The age and BMI of the subjects with the overlap syndrome were higher than those of the subjects with OSA alone. However, since even after adjustments for these covariates, the baPWV was higher in subjects with the overlap syndrome than that in the subjects with OSA alone, a longitudinal study is proposed to confirm that overlap by COPD is an important determinant of the progression of arterial stiffening in subjects with OSA; 2. Some studies have reported gender differences in the PWV,[2,3,22] but the present study was conducted only in male subjects; 3. Increased arterial stiffness is thought to act as a risk for cardiovascular disease; while the baPWV only reflects the stiffness of the large to middle-sized arteries, it shows close correlation with the carotid-femoral PWV, a gold standard for assessment of the large arterial stiffness[31]; 4. In the present study, while the serum BNP levels were higher in the patients with the overlap syndrome, the LVMI was similar between two groups. It is possible that the regression of LVMI by antihypertensive medication has some influence on this absence of difference of the LVMI between the two groups; 5. We did not evaluate whether mild/moderate COPD might predispose to daytime hypoxemia in the present study.

Conclusion

In patients with OSA, pulmonary dysfunction may be an independent risk factor for increase in arterial stiffness. Overlap by COPD (mostly mild to moderate COPD) in patients with OSA augments the increase in arterial stiffness without exaggerating nocturnal hypoxemia or inflammation. This augmentation may partially contribute to the increased cardiovascular risk in patients with the overlap syndrome.

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Conflict of interest

None declared.

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